REMARKS

Amendments to Claims

Please cancel claims 1-62 without prejudice and enter new claims 63-84 as shown above. New 63-84 claims are supported by the specification as filed, including original claims. *See, e.g.*, page 6, line 24-26; page 17, line 3; page 8, lines 6-7; page 16, lines 27-29; page 17, lines 6-7; and original claims 10, 11, 52, 53, and 57.

Formal Matters

The specification has been amended to correct a typographical error in the filing date of U.S.S.N. 60/143,228.

The specification has been further amended to include sequence identifiers for sequences disclosed on page 32 (SEQ ID NOs:23-26).

Additionally, the specification has been amended to include what the Examiner considers to be the "essential material" from Thompson et al. (2001) Science, 293:2108, incorporated by reference at page 17, lines 5-6, of the specification. The added material contains amino acids sequences for human (SEQ ID NO:27) and murine (SEQ ID NO:28) BAFF-R.

To support the above amendments, the following materials are submitted with this response: (1) a Declaration under *In re Hawkins*; (2) a paper copy of the substitute Sequence Listing, (3) a corresponding electronic copy, and (4) a

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Statement under 37 C.F.R. § 1.821(f). The substitute Sequence Listing reflects changes made in the specification, *i.e.*, the addition of SEQ ID NOs:23-28.

Figures 1A, 1B, 1C, 2A, 2B, and 6 have been amended to replace notations "KayL" and "MARCH" with the notation "BAFF." As the Examiner has noted, "KayL" and "MARCH" are alternative, less commonly used, designations for BAFF. Support for this amendment can be found, *e.g.*, on page 11, lines 3-7. Replacements sheets for Figures 1A, 1B, 1C, 2A, 2B, and 6 are submitted with this response.

No new matter has been introduced by any of the above amendments.

Rejections under 35 U.S.C. § 112, ¶1

Claims 52-53 and 57 were rejected under 35 U.S.C. § 112, ¶1, for lack of enablement and written description. These claims have been replaced by new claims 63-84. Should the same rejections be applied to the new claims, Applicants traverse for the reasons stated below.

Enablement

In the Examiner's opinion, the specification does not provide sufficient biochemical information to distinctly identify BAFF-blocking agents other than human and murine BAFF-R. According to the Examiner:

> [t]here is insufficient direction or objective evidence as to how to make and how to use any agent which diminish[es] BAFF ligand binding to BAFF-R for the number of possibilities associated with the myriad of direct and indirect effects associated with various BAFF receptors and hence pathways or molecules and, in turn, as to whether such a desired effect can be achieved or predicted, as encompassed by the claims. Office Action,

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June 30, 2003, at 4.

The Examiner contends that it would require undue experimentation for a person skilled in the art to arrive at "the other BAFF blocking agents" encompassed by the claims.

As an initial matter, Applicants respectfully point out that pending claims were restricted by the Examiner to a single class of BAFF blocking agents, *i.e.,* soluble forms of the BAFF receptor BAFF-R. *See* Restriction Requirement, March 24, 2003. Accordingly, Applicants understand the enablement rejection to apply only to the genus of soluble forms of BAFF-R, and not to all other "BAFF blocking agents."

A. Ngo

To support the contention that undue experimentation would be required, the Examiner cited Ngo et al. (The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (eds.), Birkhouser, Boston, MA, pp. 433 and 492-495. According to the Examiner, Ngo shows that the relationship between the sequence of a protein/peptide and its tertiary structure/activity is not well understood and is not predictable.

Ngo is not relevant to the present invention. Ngo addresses the problem of *theoretically predicting* the tertiary structure for a given protein based on its amino acid sequence alone. *See* Future Work, p. 492. However, in order to practice the present invention within the full scope of the claims, one does not need to *theoretically predict* the structure (or activity) of a particular BAFF-R. Instead, all that

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is necessary here is to empirically test whether a specific soluble BAFF-R binds to BAFF and blocks its function using BAFF-binding assays. These types of assays are well known to persons skilled in the art and such assays are practiced routinely. Ngo, on the other hand, does not address functional assays; it is concerned with an entirely different problem. Appropriate assays are described, for example, in Thompson et al. (2001) Science, 293:2108 (incorporated in the specification by reference at page 17, lines 5-6; copy enclosed; *see*, in particular, Supplemental Figure 3). Given that procedures for BAFF-binding assays are set forth in Thompson, the amount of experimentation involved in these assays is trivial. All one needs to do is to follow protocols shown in Thompson.

Ngo cannot be used to show that claims require undue experimentation. Therefore, the Examiner has not met his burden to make a *prime facie* showing of non-enablement. Even if the Examiner had made such a showing and the burden had shifted to the Applicants, Thompson demonstrates that the amount of experimentation required to practice the invention within the full scope of the claims is not undue.

B. Dang

The Examiner further contends "it is unpredictable whether treatment of SS [Sjögren's syndrome] with soluble BAFF-R would reach a therapeutic endpoint." To support this contention, the Examiner cited Dang et al. (1995) J. Immunol., 155(6):3205-3212, which allegedly shows that the art is unpredictable.

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Dang is not relevant to the present invention. Dang shows that administration of TGF-β to TGF-β-null mice fails to reduce autoantibody production. The claims, however, require administration of BAFF-R, and not TGF-β. TGF-β and BAFF-R are dissimilar molecules, both structurally and functionally. To illustrate this point, Applicants attach results of a comparison between human TGF-β1 (Accession No. P01137) and BAFF-R (Accession No. AF373846) sequences. These results were generated using the standard sequence comparison program "Blast 2 Sequences." *See* Appendix A. As seen from the sequence comparison, no significant similarity exists between TGF-β and BAFF-R. Likewise, there is no apparent functional similarity between the two molecules. In fact, TGF-β is a ligand of the TGF-β superfamily, whereas BAFF-R belongs to the TNF receptor family. Unlike BAFF-R, TGF-β does not bind to BAFF; TGF-β is not even a receptor. Dang does not mention BAFF, BAFF-R, or any other TNF family receptor or ligand.

In any case, whether or not TGF-β showed any effect in Dang's experiments makes no difference. Suppose, Dang did show that TGF-β had a particular effect. This would not allow a skilled artisan to conclude that BAFF-R would (or would not) have the same or a similar effect. For that reason, Dang is not useful for showing unpredictability of the art, at least as far as BAFF-mediated effects are concerned.

Therefore, Dang, like Ngo, does not support the Examiner's contention that claims require undue experimentation.

The Examiner further contends that "[t]he specification does not provide empirical data to show the efficacy of active immunization with soluble BAFF-R on

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SS, wherein the soluble BAFF-R would function to treat/reduce severity of SS." In short, the Examiner does not believe that the claimed methods would work. Applicants respectfully disagree.

The instant specification teaches that as a result of BAFF overexpression, BAFF transgenic mice develop Sjögren-like syndrome as they age. *See* Examples 7-11. The mice develop proteinuria, lupus-like disease, severe sialadenitis, and decreased saliva production. The working examples support the concept that an imbalance in BAFF production is a major factor contributing to the development of SS. This concept is further supported by the finding that many patients with primary SS have high levels of BAFF in the serum. In particular, the specification discloses high incidence (36%) of abnormally high levels of BAFF in the serum of patients with SS. *See* Example 12.

To further illustrate this point, Applicants enclose an article by Mariette et al. (2003) Ann. Rheum. Dis., 62:168-171, who also evaluated the levels of BAFF (called BLyS in Mariette) in serum from patients with primary SS. Just as disclosed in the specification, Mariette found that serum levels of BAFF are elevated in SS patients (Figure 1A). Further, Mariette statistically confirmed a correlation between the high levels of BAFF and hyper-gammaglobulinemia (Figure 2) or autoantibody levels (Figure 3). *See, also,* Discussion, p. 170. Mariette concludes by saying:

> In any case, ***it is clear from animal models that the ability to antagonise BLyS has a major impact on the manifestations of autoimmune disease.***[7 18] Analogous to anti-TNF strategies, which now have widespread application in the clinic, both monoclonal

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> antibodies and receptor fusion proteins are effective in vitro. ***The success of fusion proteins in vivo in blocking BLyS and ameliorating several autoimmune disease models raises the possibility of a novel therapeutic approach in human SS and other diseases in which BLyS may participate*** in activating specific autoreactive B cells and modulating the level of production of autoantibodies, which are the hallmark of the disease. The prospect of a new therapeutic strategy with mechanistic specificity, without widespread side effects, and with application to the more common human autoimmune diseases is very promising. Mariette, p. 170, right col., emphasis added.

Thus, Mariette provides evidence that, having the knowledge of BAFF transgenic mouse data, a skilled artisan would not reasonably doubt that the claimed methods work.

Additionally, with this response, Applicants submit a Declaration by Dr. Susan Kalled. The Declaration provides yet further evidence that BAFF antagonism improves certain physiologic parameters, as claimed. Dr. Kalled and her colleagues evaluated treatment of BAFF transgenic mice with a soluble form of a BAFF receptor, BCMA (B cell maturation antigen). Dr. Kalled provides experimental evidence that total serum Ig, splenolomegaly, and the numbers of MZ and mature B cells are significantly inhibited by the treatment with the BAFF receptor. Kalled Declaration, ¶11. These therapeutic effects are attributed to sequestration of BAFF. *Id.* Dr. Kalled further states that administration of soluble forms of other BAFF receptors, such as BAFF-R and TACI, as well as anti-BAFF antibodies, is

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similarly expected to result in a reduction in immunoglobulin production and B cell growth. *Id.*, ¶12.

In summary, Dang or Ngo, alone or in combination, do not support the Examiner's contention that claims require undue experimentation. Therefore, the Examiner has not met his burden to make a *prime facie* showing of non-enablement. Even if the Examiner had made such a showing and the burden had shifted to the Applicants, Thompson, Mariette, and Kalled show that one of skill in the art could make and use the claimed invention without undue experimentation. Accordingly, Applicants request the Examiner to withdraw the rejection under 35 U.S.C. § 112, ¶1, for lack of enablement.

Written Description

The Examiner contends that the claims do not satisfy the written description requirement. The Examiner asserts that, regardless of the method claimed, the specification shows only human and murine BAFF-R sequences as examples of BAFF blocking agents. According to the Examiner, human and mouse sequences are not enough to support the broader genus of "BAFF blocking agents" recited by the claims. Applicants respectfully traverse.

As stated above, pending claims were restricted by the Examiner to a single class of BAFF blocking agents, *i.e.*, soluble forms of the BAFF receptor BAFF-R. *See* Restriction Requirement, March 24, 2003. Accordingly, Applicants understand

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the written rejection to apply only to the genus of soluble forms of BAFF-R, and not to all other "BAFF blocking agents."

The Examiner has the initial burden of coming up with authoritative evidence showing inadequate written description. The Examiner relied on Ngo and/or Dang in rejecting claims for lack of written description. However, these references are defective for the reasons stated above in the discussion of the enablement rejection. Thus, the Examiner has not made a proper *prima facie* showing of lack of written description.

With respect to the genus of soluble BAFF-R's, human and murine BAFF-R sequences are sufficiently representative of all soluble BAFF-R forms. These sequences provide unifying structural and functional features that allow a skilled artisan to readily ascertain a substantial number of other species within the claimed genus that retain the required functional characteristics.

Human and murine BAFF-R have been previously isolated, functionally tested, and characterized. *See*, *e.g.*, Thompson et al. (2001) Science, 293:2108; incorporated in the specification by reference at page 17, lines 5-6; copy enclosed. The exact chemical identity of both receptors has been well established.

Thompson shows an alignment of the human and murine BAFF-R sequences in Figure 1. This alignment reveals common structural features of the claimed genus. As seen in Figure 1, a number of amino acids (40 out of ~80) are identical in both sequences. A simple sequence comparison by the "Blast 2 Sequences" program, demonstrates that the human and murine BAFF-R sequences possess a

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55% identity and a 60% homology in the extracellular domain of about 80 amino acids (which is the relevant domain here). *See* Appendix B.

Human and mice are phylogenetically divergent, with most other mammalian species falling between the two on the phylogenetic tree. Thompson further teaches that human BAFF-R interacts with human and murine BAFF (p. 2109, bottom of middle col.). This demonstrates that despite the difference in their primary structure, human and murine BAFF-R have a similar tertiary structure and activity. And a substantial number of other members of the genus (*e.g.*, BAFF-R from other mammalian species) are expected to possess this functionality/structure because their identity levels in the extracellular domain would be similar to that between mouse and human, or higher. To further illustrate this point, Applicants submit an excerpt from Fersht (Structure and Mechanism in Protein Science, W. H. Freeman and Company, N.Y., 1998, pages 33-34) which states:

> An important question is: What is the relationship between percent identity and similarity of tertiary structure? This depends on the length of the protein: the longer the protein, the lower the percent identity that implies identical structure. ***For a protein of 85 residues, a 25 to 30% sequence identity implies an identical three-dimensional structure.*** Fersht, p. 34, emphasis added.

To recap: (1) an alignment of human and mouse sequences reveals unifying structural features of the claimed genus; (2) human and murine BAFF-R exhibit a 55% identity in the extracellular domain of about 80 amino acids; (3) Fersht teaches that tertiary structure of these two proteins is expected to be identical and Thompson

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confirms that human and murine BAFF-R do, in fact, have the same functionality (*i.e.*, they both bind to murine BAFF); (4) human and mouse are phylogenetically divergent, with most other BAFF-R species being expected to have a similar or higher percent identity than that between human and murine sequences; and (5) according to Fersht, a substantial number of BAFF-R species are expected to retain the tertiary structure/activity required by the claimed methods. Therefore, human and murine sequences are representative of the claimed genus of soluble BAFF-R.

In summary, the Examiner has not met his burden to make a *prima facie* showing of lack written description. Even if the Examiner had made such a showing and the burden had shifted to the Applicants, Thompson and Fersht demonstrate that the specification provides adequate description for the claims. Accordingly, Applicants request the Examiner to withdraw the written description rejection.

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration of this application and the timely allowance of the pending claims. Should the Examiner require further clarification, the Examiner is welcome to call the undersigned at (617) 452-1650.

Please grant any extensions of time required to enter this response and charge any additional required fees to deposit account 06-0916.

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Respectfully submitted,

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APPENDIX A

NCBI **BLAST 2 sequences** BLAST Entrez ?

This tool produces the alignment of two given sequences using BLAST engine for local alignment.

Program blastn Align

Sequence 1: from: to:

Enter sequence in FASTA format

```
MPPSGLRLLL LLLPLLWLLV LTPGRPAAGL STCKTIDMEL
VKRKRIEAIR GQILSKLRLA SPPSQGEVPP GPLPEAVLAL
YNSTRDRVAG ESAEPEPEPE ADYYAKEVTR VLMVETHNEI
YDKFKQSTHS IYMFFNTSEL REAVPEPVLL SRAELRLLRL
KLKVEQHVEL YQKYSNNSWR YLSNRLLAPS DSPEWLSFDV
TGVVRQWLSR GGEIEGFRLS AHCSCDSRDN TLQVDINGFT
```

or download from file

Sequence 2: from: to:

Enter sequence in FASTA format

```
MRRGPRSLRG RDAPAPTPCV PAECFDLLVR HCVACGLLRT
PRPKPAGASS PAPRTALQPQ ESVGAGAGEA ALPLPGLLFG
APALLGLALV LALVLVGLVS WRRRQRRLRG ASSAEAPDGD
KDAPEPLDKV IILSPGISDA TAPAWPPPGE DPGTTPPGHS
VPVPATELGS TELVTTKTAG PEQQ
```

or download from file

Parameters used in BLASTN program only:

Reward for a match: 1 **Penalty for a mismatch:** -2

Matrix Not Applicable Open gap 5 and extension gap 2 penalties

Gap x_dropoff 50 Expect value 10 Word size 11 Filter ☑

Align Reset form

Comments and suggetstions to: blast-help@ncbi.nlm.nih.gov

NCBI

Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.6 [Apr-09-2003]

Matrix BLOSUM62 gap open: 11 gap extension: 1

x_dropoff: 50 expect: 10.0(wordsize: 3 Filter Align

Sequence 1 lcl|seq_1 **Length** 390

Sequence 2 lcl|seq_2 **Length** 184

No significant similarity was found

APPENDIX B

NCBI

Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

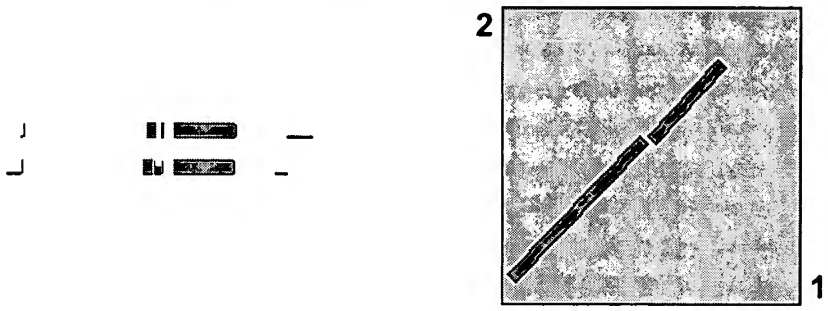
BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.6 [Apr-09-2003]

Matrix BLOSUM62 gap open: 11 gap extension: 1

x_dropoff: 50 expect: 10.0(wordsize: 3 Filter ☑ Align

Sequence 1 lcl|seq_1 **Length** 80 (1 .. 80)

Sequence 2 lcl|seq_2 **Length** 76 (1 .. 76)



NOTE:The statistics (bitscore and expect value) is calculated based on the size of nr database

```
Score = 58.5 bits (140), Expect = 3e-08
Identities = 31/56 (55%), Positives = 34/56 (60%), Gaps = 2/56 (3%)
```

```
Query:  5  RSLRGRDAPAPTPCVPAECFDLLVRHCVACGLLRTPRPKPAGASSPAPRTALQPQE 60
           RS R RD+  PT C   ECFD LVR+CV+C L  T  P     SS  P TALQPQE
Sbjct:  9  RSQRSRDSSVPTQCNQTECFDPLVRNCVSCELFHT--PDTGHTSSLEPGTALQPQE 62
CPU time:     0.01 user secs.     0.01 sys. secs         0.02 total secs.

Lambda      K       H
   0.321    0.138    0.452

Gapped
Lambda      K       H
   0.267   0.0410    0.140


Matrix: BLOSUM62
Gap Penalties: Existence: 11, Extension: 1
```

```
Number of Hits to DB: 57
Number of Sequences: 0
Number of extensions: 5
Number of successful extensions: 2
Number of sequences better than 10.0: 1
Number of HSP's better than 10.0 without gapping: 1
Number of HSP's successfully gapped in prelim test: 0
Number of HSP's that attempted gapping in prelim test: 0
Number of HSP's gapped (non-prelim): 1
length of query: 80
length of database: 519,293,288
effective HSP length: 56
effective length of query: 24
effective length of database: 519,293,232
effective search space: 12463037568
effective search space used: 12463037568
T: 9
A: 40
X1: 16 ( 7.4 bits)
X2: 129 (49.7 bits)
X3: 129 (49.7 bits)
S1: 41 (21.9 bits)
S2: 67 (30.4 bits)
```